1,129,029

PATENT SPECIFICATION

NO DRAWINGS

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Date of Application and filing Complete Specification: 8 March, 1967.

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Application made in Germany (No. B86165 IVb/12o) on 11 March, 1966.

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Index at acceptance:—C2 C(2A2, 2A3, 2A5, 2A12, 2A14, 2R15, 2T16, 3A14A2A, 3A14A7A, 3A14A7B, 3A14A7C, LF22X, LF29X, LF29Y, LF32Y, LF36Y, LF45Y, LF200, LF213, LF253, LF254, LF321, LF360, LF363, LF451, LF662, LF672, LM22X, LM29X, LM29Y, LM32Y, LM36Y, LM321, LM351, LM353, LM360, LM363, LM650, LM662, MB22X, MB36Y, MB200, MB213, MB253, MB254, MB326, MB351, MB353, MB360, MB363, MB656, MB662, MB672, MD22X, MD326, MD351, MD353, MD656)

Int. Cl.:—C 07 c 87/00, C 07 d 7/42, C 07 d 65/16

COMPLETE SPECIFICATION

Tricyclic Ethylamine Derivatives

We, C. F. BOEHRINGER & SOEHNE [illegible] G.M.B.H., of Mannheim-[illegible] Rod[illegible]

ERRATA

SPECIFICATION No. 1,129,029

Page 4, line 12, *for* "ther" *read* "there"
Page 6, *for* "cynaomethyl-fluorene" (first occurrence) *read* "cyanomethyl-fluorene"
Page 8, second column of Table III, *for* "varient" *read* "variant"
Page 10, line 23, *for* "10.2 mm." *read* "0.2 mm."
Page 14, line 59, *for* "10.1 mm." *read* "/0.1 mm."
Page 15, line 18, *for* "wit" *read* "with"
Page 15, line 22, *for* "10.2 mm." *read* "0.2 mm."
Page 15, line 97, *for* "-ethiepine." *read* "-thiepine"

THE PATENT OFFICE
9th December 1968

[illegible]ssess are [illegible]opic [illegible] pre- [illegible], in [illegible]eral

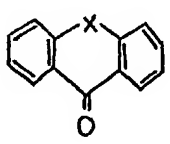
[illegible]$_2$[illegible]$_2$

(I)

wherein X is an oxygen or sulphur atom or a saturated or unsaturated, straight or branched chain hydrocarbon radical containing 2 or 3 carbon atoms or an oxaethylene, thiaethylene, thiapropylene or carbonyl group or a valency bond, R_3 is a hydrogen atom or an alkyl radical containing up to 3 carbon atoms, R_1 is a hydrogen atom or a hydroxyl group and R_2 is a hydrogen atom or R_1 and R_2 together represent a further valency bond, with the proviso that when X is an ethylene radical, then R_1 and R_2 are either both hydrogen atoms or together form a further valency bond.

We have found that the new compounds [illegible] obtained [illegible] formula (I), in the case of which R_1 is a hydroxyl group, are then, if desired, subsequently dehydrated or, in the case in which R_1 and R_2 represent an additional valency bond, are then, if desired, subsequently hydrogenated.

The nitriles of general formula (II) used as starting materials are new compounds. They can be obtained by a type of aldol condensation from tricyclic ketones of the general formula:—



(III)

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SEE ERRATA SLIP ATTACHED

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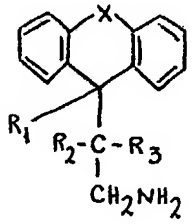
COMPLETE SPECIFICATION

Tricyclic Ethylamine Derivatives

We, C. F. BOEHRINGER & SOEHNE G.M.B.H., of Mannheim-Waldhof, Germany, a Body Corporate organised under the laws of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new tricyclic ethylamine derivatives and with the preparation thereof.

The new tricyclic ethylamine derivatives according to the present invention are compounds of the general formula:—

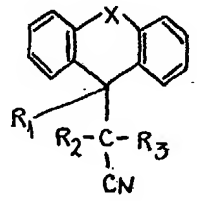


(I)

wherein X is an oxygen or sulphur atom or a saturated or unsaturated, straight or branched chain hydrocarbon radical containing 2 or 3 carbon atoms or an oxaethylene, thiaethylene, thiapropylene or carbonyl group or a valency bond, R_3 is a hydrogen atom or an alkyl radical containing up to 3 carbon atoms, R_1 is a hydrogen atom or a hydroxyl group and R_2 is a hydrogen atom or R_1 and R_2 together represent a further valency bond, with the proviso that when X is an ethylene radical, then R_1 and R_2 are either both hydrogen atoms or together form a further valency bond.

We have found that the new compounds (I) according to the present invention possess valuable pharmacological properties and are characterised, in particular, by psychotropic and circulatory-stimulating actions.

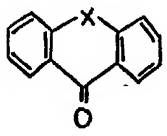
The new compounds according to the present invention can be prepared by reducing, in known manner, compounds of the general formula:—



(II)

in which R_1, R_2, R_3 and X have the same meanings as above, the compounds obtained of general formula (I), in the case of which R_1 is a hydroxyl group, are then, if desired, subsequently dehydrated or, in the case in which R_1 and R_2 represent an additional valency bond, are then, if desired, subsequently hydrogenated.

The nitriles of general formula (II) used as starting materials are new compounds. They can be obtained by a type of aldol condensation from tricyclic ketones of the general formula:—



(III)

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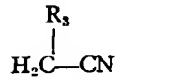
in which X has the same meaning as above, with nitriles of the general formula:—



(IV)

in which R_3 has the same meaning as above, in the presence of a basic condensation agent, preferably of lithium amide in liquid ammonia, whereupon the hydroxy-nitriles (II) obtained (R_1 = OH; R_2 = H) are, if desired, subsequently dehydrated to the corresponding unsaturated nitriles (II) (R_1 and R_2 together form another valency bond) which in turn can, if desired, be selectively hydrogenated with aluminium amalgam to give the corresponding saturated nitriles (R_1 = R_2 = H).

The reduction of the nitriles (II) to the corresponding amines (I) is carried out in known manner. For this purpose, it is preferable to use complex metal hydrides, such as lithium aluminium hydride, especially when R_1 and R_2 are to represent a further valency bond in the end product. In principle, however, the hydrogenation can also be carried out catalytically and, in the case in which X is a carbonyl group, it is even preferred to carry out the hydrogenation without the use of pressure, for example, in the presence of Raney nickel.

Since the hydrogenation of the compounds (I) to the compounds (II) can be carried out selectively, a nitrile (II) is, in general, used as starting material in which R_1 and R_2 have the significance desired in the end product. However, for the preparation of compounds (I) in which R_1 and R_2 represent hydrogen atoms, it is also possible to start from the unsaturated nitriles (II) (R_1 and R_2 together represent a further valency bond) and, in one or two steps, to hydrogenate these twice, i.e. not only at the double bond but also at the nitrile group. Since the C=C double bond is, in general, not attacked or only slowly attacked by complex metal hydrides, such as lithium aluminium hydride, it is recommended, in such cases, to hydrogenate catalytically the double bond and the nitrile group in one step. When, as end products, it is desired to obtain those tricyclic ethylamines (I) in which R_1 and R_2 are either both hydrogen atoms or together form a further valency bond, then it is also possible to start from hydroxy-nitriles (II) (R_1 = OH) and to get the desired end products by subsequently splitting off the elements of water and, if desired, thereafter hydrogenating the double bond.

The following Examples are given for the purpose of illustrating the present invention:—

A) Preparation of compounds (I) in which R_1 is a hydroxyl group and R_2 is a hydrogen atom from nitriles (II) in which R_1 is a hydroxyl group and R_2 is a hydrogen atom.

EXAMPLE 1.

9-hydroxy-9-(2-aminoethyl)-thiaxanthene.

18.5 g. (0.07 mol) 9-hydroxy-9-cyanomethyl-thiaxanthene are substantially completely dissolved in 150 ml. ether and slowly added dropwise, with stirring and external cooling, to a suspension of 3.8 g. (0.1 mol) lithium aluminium hydride in 50 ml. ether. The reaction mixture is subsequently vigorously stirred for 2 hours at room temperature and then carefully decomposed by the addition of a saturated aqueous solution of sodium chloride. The precipitated metal hydroxides agglomerate and, in this form, can be filtered off with suction. The filter cake is thoroughly washed through with ether, the combined ethereal filtrates dried over anhydrous potassium carbonate and ethereal hydrochloric acid added thereto dropwise in order to obtain 9-hydroxy-9-(2-aminoethyl)-thiaxanthene in the form of the hydrochloride. The yield is 17.0 g. (82% of theory) and the compound has a melting point of 180°C. After recrystallisation from isopropanol, the yield drops to 12.5 g. (61% of theory) and the melting point increases to 188°C.

EXAMPLES 2—15.

The compounds set out in the following Table I are obtained in a manner analogous to that described in Example 1, using the reaction conditions indicated in the Table.

The following abbreviations are used in Table I and in the subsequent Tables:

B	=	benzene
Benz	=	benzine of boiling range 53—73°C.
PF	=	petroleum fraction of boiling range 100—140°C.
Isopr	=	isopropanol
A	=	ethanol
Hex	=	hexane
Ae	=	ether
THF	=	tetrahydrofuran
EA	=	ethyl acetate
RT	=	room temperature
Rfl	=	reflux boiling

TABLE I

Compound	solvent	reaction time in hours	nitrile mol	$LiAlH_4$ mol	temp. °C.	m.p. of base °C.	m.p. of HCl °C.	yield
9-hydroxy-9-(2-aminoethyl)-fluorene	Ae	2	0.1	0.1	RT	114°	—	52%
5-hydroxy-5-(2-aminoethyl)-5H-dibenzo-[a,d]-cycloheptene	THF	2	0.1	0.15	RT	156—158°	—	82%
11-hydroxy-11-(2-aminoethyl)-6,11-dihydro-dibenzo-[b,e]-oxepine	Ae + THF	2	0.4	0.44	RT	—	110—115°	69% (HCl)
11-hydroxy-11-(2-aminoethyl)-6,11-dihydro-dibenzo-[b,e]-thiepine	Ae + THF	2	0.055	0.1	0.5°	118—119°	113—115°	58% (HCl)
12-hydroxy-12-(2-aminoethyl)-5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene	Ae + THF	1	0.086	0.12	38—40°	—	190—200°	44% (HCl)
12-hydroxy-12-(2-aminoethyl)-7,12-dihydro-6H-dibenzo-[b,e]-thiocine	Ae + THF	2	0.075	0.1	RT	—	208°	50%
10-hydroxy-10-(2-aminoethyl)-anthrone	A/H_2 Raney Ni	5	0.056	2.5 g Raney Ni	40—50°	—	184—185°	68.5% (HCl)
9-hydroxy-9-(1-aminobutyl-2)-fluorene	Ae	2	0.102	0.15	Rfl.	—	215°	83.5%

TABLE I (Continued)

Compound	solvent	reaction time in hours	nitrile mol	$LiAlH_4$ mol	temp. °C.	m.p. of base °C.	m.p. of HCl °C.	yield
9-hydroxy-9-(1-aminobutyl-2)-xanthene	Ae	1	0.127	0.191	Rfl.	134—135°	—	79.5%
9-hydroxy-9-(1-amino-butyl-2)-thiaxanthene	Ae	1	0.1	0.15	Rfl.	—	204—205°	81.5%
5-hydroxy-5-(1-aminobutyl-2)-5H-dibenzo-[a,d]-cycloheptene	Ae/THF	1	0.1	0.15	Rfl.	139—140°	294° (dec.)	70.4%
11-hydroxy-11-(1-aminobutyl-2)-6,11-dihydro-dibenzo-[b,e]-oxepine	Ae/THF	2	0.072	0.105	10°	—	227—228°	69.5%
11-hydroxy-11-(1-aminobutyl-2)-6,11-dihydro-dibenzo-[b,e]-thiepine	Ae/THF	2	0.112	0.16	RT	—	253°	54%
12-hydroxy-12-(1-aminobutyl)-2)-5,6,7,12-tetra-hydro-dibenzo-[a,d]-cyclooctene	Ae	1	0.0276	0.04	Rfl.	—	249—250°	—

The nitriles (II) in which R_1 is a hydroxyl group and R_2 is a hydrogen atom, which are used as starting materials, can be prepared in the following ways:

Variant a:
11-hydroxy-11 - cyanomethyl - 6,11-dihydro-dibenzo-[b,e]-oxepine, with the use of sodamide in liquid ammonia.

In a three-necked flask, provided with a solid carbon dioxide-methanol reflux cooler, ground-in stirrer and dropping funnel, ther is prepared a solution of sodamide by the addition of 2.3 g. (0.1 mol) sodium and a few particles of ferric nitrate to 100 ml. liquid ammonia. After the complete disappearance of the blue colour, 3.08 g. (0.075 mol) acetonitrile are quickly added dropwise and, immediately thereafter, the reaction mixture is mixed portionwise with 10.5 g. (0.05 mol)

6,11-dihydro - dibenzo-[b,e]-oxepin-11-one. The reaction mixture is stirred for 2 hours at the reflux temperature of the boiling ammonia. The sodium derivative of the 11-hydroxy-11-cyanomethyl compound formed in this way is subsequently decomposed by the addition of 6.4 g. (0.12 mol) ammonium chloride. After the removal of the solid carbon dioxide cooler and the addition of 80 ml. ether, the ammonia is allowed to evaporate off overnight. Inorganic material is filtered off with suction and the ethereal solution evaporated. The residue (9.55 g; 76.1% of theory) still contains small amounts of starting material. By recrystallisation from benzene, the desired product is isolated in pure form. The yield is 4.1 g. (32.8% of theory) 11-hydroxy-11-cyano - methyl-6,11 - dihydro - dibenzo-[b,e]-oxepine with a melting point of 147—148°C.

Variant b:

11-hydroxy-11 - cyanomethyl-6,11 - dihydro-dizenzo-[b,e]-oxepine, with the use of lithium amide in liquid ammonia.

In a manner analogous to that described in Variant a, a solution of lithium amide is prepared in a three-necked flask from 1.38 g. (0.2 mol) lithium in 200 ml. ammonia. Subsequently, a solution of 21.0 g. (0.1 mol) 6,11-dihydro-dibenzo-[b,e]-oxepine and 8.2 g. (0.2 mol) acetonitrile in 40 ml. ether is added dropwise. After a reaction time of two hours, 24.0 g. ammonium chloride are introduced into the reaction mixture. The ammonia is allowed to evaporate overnight from the open flask. After the addition of a further amount of ether, and filtering off the inorganic material with suction, the ethereal solution is evaporated to give 24.5 g. of crude product from which, by recrystallisation in the manner described in Variant a, there are obtained 22.6 g. (90.5% of theory) of pure 11-hydroxy-11-cyanomethyl - 6,11-dihydro - dibenzo-[b,e]-oxepine with a melting point of 147—148°C.

The following nitriles in which R_1 is a hydroxyl group and R_2 is a hydrogen atom, which are also used as starting materials, can be obtained in an analogous manner, the reaction conditions set out in Table II thereby being used.

TABLE II

Compound	ketone (mol)	nitrile (mol)	metal amide (mol)	NH_3 (mol)	m.p. °C.	solvent	yield crude	yield pure
9-hydroxy-9-cynaomethyl-fluorene	0.15	0.225	0.3 Na	300	110—111	benz	96%	65%
9-hydroxy-9-cyanomethyl-xanthene	0.2	0.4	0.4 Li	750	137—138	benz	91%	73%
9-hydroxy-9-cyanomethyl-thiaxanthene	0.3	0.6	0.6 Li	1200	127—128	PF	—	77%
5-hydroxy-5-cyanomethyl-5H-dibenzo-[a,d]-cycloheptene	0.2	0.4	0.4 Li	400	202—204	A	90%	73%
11-hydroxy-11-cyanomethyl-6,11-dihydro-dibenzo-[b,e]-thiepine	0.05	0.1	0.1 Li	150	119—120	B/hex	87%	53%
12-hydroxy-12-cyanomethyl-5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene	0.1	0.1	0.1 Li	500	161—163	isopr	66.5%	46%
12-hydroxy-12-cyanomethyl-7,12-dihydro-6H-dibenzo-[b,e]-thiocine	0.1	0.1	0.1 Li	300	143—145	A	57.7%	—
10-hydroxy-10-cyanomethyl-anthrone	0.15	0.3	0.3 Na	750	170—171	isopr	—	64.5%

TABLE II (Continued)

Compound	ketone (mol)	nitrile (mol)	metal amide (mol)	NH_3 (mol)	m.p. °C.	solvent	yield crude	yield pure
9-hydroxy-9-(1-cyanopropyl-1)-fluorene	0.15	0.3	0.3 Na	300	133—135	PF	95%	83%
9-hydroxy-9-(1-cyanopropyl-1)-fluorene	0.15	0.3	0.3 Li	500	133	—	92%	—
9-hydroxy-9-(1-cyanopropyl-1)-xanthene	0.15	0.225	0.3 Li	500	106—107	PF	~100%	—
9-hydroxy-9-(1-cyanopropyl-1)-thiaxanthene	0.15	0.3	0.3 Li	500	103—104	isopr	95%	—
5-hydroxy-5-(1-cyanopropyl-1)-5H-dibenzo-[a,d]-cycloheptene	0.15	0.3	0.3 Li	400	161—162	A	92%	—
11-hydroxy-11-(1-cyanopropyl-1)-6,11-dihydro-dibenzo-[b,e]-oxepine	0.1	0.2	0.2 Li	300	158—159	B	95%	65%
11-hydroxy-11-(1-cyanopropyl-1)-6,11-dihydrodibenzo-[b,e]-thiepine	0.15	0.3	0.3 Li	500	—	—	—	—
12-hydroxy-12-(1-cyanopropyl-1)-5,6,7,12-tetrahydro-dibenzo [a,d]-cyclooctene	0.15	0.3	0.3 Li	300	115—116	isopr	—	36%

B) Preparation of compounds (I) in which R_1 and R_2 together form an additional valency bond from compounds (I) in which R_1 is a hydroxyl group and R_2 is a hydrogen atom by subsequent dehydration.

EXAMPLE 16.

11-(1 - aminobutylidene-2)-6,11 - dihydro-dibenzo-[b,e]-oxepine.
(*Variant* 1).

12 g. (0.0376 mol) 11-hydroxy-11-(1-

aminobutyl-2)-6,11-dihydro - dibenzo-[b,e]-oxepine hydrochloride, prepared as described in A), in 50 ml. alcohol which has been saturated at room temperature with hydrogen chloride, are heated to the boil for one hour. After cooling, there crystallises out 6.8 g. of the analytically pure hydrochloride of 11-(1-aminobutylidene - 2)-6,11-dihydro - dibenzo-[b,e]-oxepine with a melting point of 223—224°C. A further 3 g. of the desired product are obtained by partial evaporation of the mother liquor and subsequent recrystallisation from isopropanol. The total yield is 86.7% of theory.

EXAMPLE 17.

5-(1 - aminobutylidene-2) - dibenzo - [a,d]-cycloheptene.

(*Variant* 2).

11.3 g. 5-hydroxy-5-(1 - aminobutyl-2)-dibenzo-[a,d]-cycloheptene (0.0405 mol), prepared as described in A), are dissolved in 100 ml. 48% hydrobromic acid and heated for one hour on a boiling water bath. After the addition of excess sodium hydroxide solution, the base is extracted with ether and purified by high vacuum distillation. There are obtained 7.2 g. (68% of theory) 5-(1-aminobutylidene-2)-dibenzo-[a,d]-cycloheptene in the form of a pale, yellowish oil with a boiling point of 160—162°C./0.2 mm.Hg. The hydrochloride thereof, after recrystallisation from isopropanol, melts at 194—195°C.

EXAMPLES 18—30.

The following compounds are obtained in a manner analogous to that described in Example 16 or 17, the reaction conditions used being those set out in Table III.

TABLE III

Compound	varient	solvent	reaction time (hrs)	temp. °C.	m.p. of HCl °C.	yield
9-(1-aminoethylidene)-fluorene	1	A/HCl	½	Rfl	268—270	60.1%
9-(1-aminoethylidene)-xanthene	1	A/HCl	½	RT	175	93%
9-(1-aminoethylidene)-thia-xanthene	1	A/HCl	1	Rfl	183—184	90.2%
5-(1-aminoethylidene)-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	1	A/HCl	1	Rfl	208—209	59.5%
5-(1-aminoethylidene)-5H-dibenzo-[a,d]-cycloheptene	1	A/HCl	1	Rfl	232—233	65.5%
11-(1-aminoethylidene)-6,11-dihydro-dibenzo-[b,e]-oxepine	1	A/HCl	1	Rfl	235—237	37.1%
11-(1-aminoethylidene)-6,11-dihydro-dibenzo-[b,e]-thiepine	1	A/HCl	1	Rfl	217—218	83.0%
12-(1-aminoethylidene)-5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene	1	A/HCl	1	Rfl	243—245	47.5%
9-(1-aminobutylidene-2)-fluorene	2	48% HBr glacial acetic acid	2	100	239	91.0%
9-(1-aminobutylidene-2)-thia-xanthene	1	A/HCl	1	Rfl	232—233	84.0%

TABLE III (Continued)

Compound	variant	solvent	reaction time (hrs)	temp. °C.	m.p. of HCl °C.	yield
5-(1-aminobutylidene-2)-10,11-dihydro-5H-dibenzo[a,d]-cycloheptene	1	A/HCl	1	Rfl	219—220	79.5%
11-(1-aminobutylidene-2)-6,11-dihydro-dibenzo-[b,e]-thiepine	1	A/HCl	1	Rfl	267	93.5%
12-(1-aminobutylidene-2)-5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene	1	A/HCl	1	Rfl	271—272	78.5%

C) Preparation of compounds (I) in which R_1 and R_2 together form an additional valency bond from compounds (II) in which R_1 and R_2 together form an additional valency bond.

EXAMPLE 31.

5-(1-aminobutylidene-2) - 10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

5.9 g. (1-cyanopropylidene - 1) - 10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene (0.023 mol) are boiled under reflux for 2 hours in ethereal solution (100 ml.) with 1.14 g. lithium aluminium hydride (0.03 mol). After the careful addition of a saturated aqueous sodium chloride solution, the precipitated hydroxides are filtered off with suction, the ethereal solution is dried and the basic material is precipitated therefrom as the hydrochloride. After dissolving in alcohol and again precipitating the product by the addition of ether, there are obtained 4.8 g. (70.6% of theory) of analytically pure 5-(1-aminobutylidene-2)-10,11-dihydro - 5H - dibenzo-[a,d] - cycloheptene with a melting point of 224—225°C.

EXAMPLES 32—35.

The following compounds are obtained in a manner analogous to that described in Example 31, the reaction conditions set out in Table IV being used.

TABLE IV

Compound	reaction time (hrs)	temp. °C.	nitrile (mol)	$LiAlH_4$ (mol)	b.p. of base °C.	m.p. of HCl °C.	yield
5-(1-aminoethylidene)-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	2	0—5	0.05	0.11	151—152/0.15	208—210 isopr	73%
11-(1-aminoethylidene)-6,11-dihydro-dibenzo-[b,e]-oxepine	2	—10	0.05	0.11	—	235—237	56%
9-(1-aminobutylidene-2)-xanthene	2½	—10	0.044	0.088	—	187—188	49%
5-(1-aminobutylidene-2)-5H-dibenzo-[a,d]-cycloheptene	1	40	0.02	0.026	157—160/0.2	—	76.4%

The nitriles (II) in which R_1 and R_2 together form an additional valency bond and which are used as starting materials, can be prepared in the following ways by dehydration of nitriles (II) in which R_1 is a hydroxy group and R_2 is a hydrogen atom.

Variant a:

5 - cyanomethylene - 5H - dibenzo - [a,d]-cycloheptene.

10 g. 5-hydroxy - 5 - cyanomethyl - 5H-dibenzo-[a,d]-cycloheptene (0.0405 mol), prepared according to A), are heated to boiling

for one hour in 150 ml. isopropanol saturated with hydrogen chloride. Subsequently, the reaction mixture is evaporated to give 9.0 g. of a residue with a melting point of 137—138°C. This product is recrystallised from a petroleum fraction with a boiling range of 100—140°C. There are obtained 7.2 g. (79% of theory) of analytically pure crystals of 5-cyanomethylene-5H - dibenzo-[a,d] - cycloheptene with a melting point of 143—144°C.

Variant b:

9-(1-cyanopropylidene-1)-xanthene.

13 g. 9-hydroxy-9 - (1-cyanopropyl - 1)-xanthene, prepared according to A), are well mixed with 25 g. phosphorus pentoxide and heated to 150°C. for one hour on an oil bath. After the careful addition of 300 ml. water, the reaction mixture is extracted with ether. After evaporation of the ethereal extract, there are obtained 10.5 g. (86.8% of theory) of a yellowish-red oil which slowly crystallises. When subjected to high vacuum distillation, it boils at 160—162°C./10.2 mm.Hg. From 9 g. of this red oil, there are obtained, after boiling up with benzine, 7.0 g. (57.8% of theory) of analytically pure 9-(1-cyanopropylidene-1)-xanthene with a melting point of 82—83°C.

Variant c:

12-cyanomethylene - 5,6,7,12 - tetrahydro-dibenzo[a,d]-cyclooctene.

14.8 g. 12 - hydroxy - 12 - cyanomethyl-5,6,7,12-tetra-hydro-dibenzo - [a.d] - cyclooctene, prepared according to A), are, in the form of crude product (86% of the calculated nitrogen value) dissolved in 100 ml. alcoholic hydrochloric acid, boiled for one hour under reflux and, after evaporation, subjected to a high vacuum distillation. The first runnings consist mainly of 5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene-12-one (4.5 g.; b.p. 173—178°C./0.8 mm.Hg.), while the main fraction of 7.5 g. (63% of theory; b.p. 182—183°C./0.8 mm.Hg.) consists of the desired product, i.e. 12-cyano-methylene-5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene, which, after recrystallisation from benzine, has a melting point of 64—65°C.

The following nitriles (II) used as starting materials, in which R_1 and R_2 together form an additional valency bond, are prepared in an analogous manner, the reaction conditions set out in Table V thereby being used.

TABLE V

Compound	dehydration agent	reaction time (hrs)	temp. °C.	b.p. °C.	m.p. °C.	yield
9-cyanomethylenefluorene	P_2O_5	½	160	155—164/ 0.05	110—111	78.1%
9-cyanomethylenexanthene	A/HCl	1	Rfl	196—200/ 0.4	134—135	87.4%
9-cyanomethylene-thiaxanthene	A/HCl	1	Rfl	—	156—158	91.1%
5-cyanomethylene-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptane	A/HCl	1	Rfl	—	105—106	81.0%
11-cyanomethylene-6,11-dihydro-dibenzo-[b,e]-oxepine	A/HCl	1	Rfl	—	150—151	67.6%
11-cyanomethylene-6,11-dihydro-dibenzo-[b,e]-thiepine	A/HCl	1	Rfl	—	176—177	83.5%
10-cyanomethyleneanthrone	oxalic acid	20 min.	140	—	191—192	60.0%
9-(1-cyanopropylidene-1)-fluorene	P_2O_5	½	150	170—171/ 0.1	77—78	92.0%
9-(1-cyanopropylidene-1)-xanthene	A/HCl	1	Rfl	170—175/ 0.1	79—80	80.5%
9-(1-cyanopropylidene-1)-thiaxanthene	A/HCl	1	Rfl	—	106—107	85.5%
5-(1-cyanopropylidene-1)-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	A/HCl	1	Rfl	173—185/ 0.1	86—88	89.5%
5-(1-cyanopropylidene-1)-5H-dibenzo-[a,d]-cycloheptene	P_2O_5	1	160—170	—	141—142	74.5%
11-(1-cyanopropylidene-1)-6,11-dihydro-dibenzo[b,e]-oxepine	A/HCl	1	Rfl	—	126—127	73.5%
11-(1-cyanopropylidene-1)-6,11-dihydro-dibenzo-[b,e]-thiepine	A/HCl	½	Rfl	—	112—113	62.5%

D) Preparation of compounds (I) in which R_1 and R_2 are both hydrogen atoms from nitriles (II) in which R_1 and R_2 are both hydrogen atoms.

EXAMPLE 36.

11-(1-aminobutyl-2)-6,11 - dihydro - dibenzo-[b,e]-oxepine.

17.5 g. 11-(1-cyanopropyl-1)-6,11-dihydro-dibenzo-[b,e]-oxepine (0.0667 mol) in 150 ml. ether are added dropwise at 0—5°C., with good stirring, to a suspension of 3.8 g. lithium aluminium hydride in ether (0.1 mol). After a reaction time of two hours, the reaction mixture is decomposed at 5—10°C. by the addition of a saturated aqueous solution of sodium chloride, the separated hydroxides filtered off with suction and the ethereal solution dried. By the addition thereto of ethereal hydrochloric acid, the base is precipitated out in the form of its hydrochloride.

After recrystallisation from isopropanol, there are obtained 17.5 g. 11-(1-aminobutyl-2)-6,11-dihydro-dibenzo-[b,e]-oxepine (87% of theory) in the form of its hydrochloride; m.p. 219—220°C.

EXAMPLE 37.

9-(2-aminoethyl)-xanthene.

After the addition of 2 g. platinum oxide, 45 g. (0.21 mol) 9-cyanomethyl-xanthene in a mixture of 500 ml. glacial acetic acid and 5 ml. concentrated sulphuric acid are catalytically hydrogenated for 4 hours without the use of pressure. Subsequently, the acetic acid is substantially removed in a vacuum (about $\frac{3}{4}$ of its volume). The residue is taken up in water and the neutral products are removed by extraction with ether. The basic products are then liberated by the addition of 2N sodium hydroxide solution and isolated by extraction with ether. The evaporation residue of the ethereal solution gives, after a high vacuum distillation, 28.4 g. (60% of theory) 9-(2-aminoethyl)-xanthene with a boiling point of 145—148°C./0.5 mm.Hg.

EXAMPLE 38.

9-(1-aminobutyl-2)-xanthene.

22 g. 9-(1-cyanopropyl-1)-xanthene (0.0885 mol) are reduced by heating under reflux for two hours in 350 ml. anhydrous ether with 5.05 g. lithium aluminium hydride (0.133 mol). The reaction mixture is thereafter decomposed with a solution of sodium chloride and the desired product isolated by immediately precipitating the hydrochloride from the filtered ethereal solution. There are thus obtained 25.5 g. (98% of theory) 9(1-aminobutyl-2)-xanthene hydrochloride with a melting point of 251—252°C.

EXAMPLES 39—48.

The following compounds are obtained in a manner analogous to that described in Examples 36 to 38, the reaction conditions set out in Table VI thereby being used.

TABLE VI

Compound	reaction time (hrs)	temp. °C.	solvent	nitrile (mol)	reduction agent	b.p. °C.	m.p. salt °C.	yield
9-(2-aminoethyl-1)-fluorene	32	RT	A	0.1	5 g. RaNi/H_2	131—135/0.2	233—234 HCl	82.5%
9-(2-aminoethyl)-xanthene	1	Rfl	THF/Ae	0.05	0.075 mol $LiAlH_4$	—	166—167 maleate	57.5%
9-(2-aminoethyl)-thiaxanthene	2	Rfl.	THF/Ae	0.154	0.24 mol $LiAlH_4$	160—162/0.3	180 maleate	78%
5-(2-aminoethyl)-10,11-dihydro-5H-di-benzo-[a,d]-cycloheptene	2	Rfl	Ae	0.095	0.143 mol $LiAlH_4$	148—149/0.1	237—238 HCl	84.0%
5-(2-aminoethyl)-5H-dibenzo-[a,d]-cycloheptene	1	35	THF/Ae	0.025	0.035 mol $LiAlH_4$	—	238—240 HCl	80.0%
11-(2-aminoethyl)-6,11-dihydro-5H-dibenzo-[b,e]-oxepine	3	0—10	THF/Ae	0.0426	0.086 mol $LiAlH_4$	163—164/0.3	156 maleate	81.0%
11-(2-aminoethyl)-6,11-dihydro-dibenzo-[b,e]-thiepine	1	RT	THF/Ae	0.3	0.45 mol $LiAlH_4$	—	251—252 HCl	67%
9-(1-aminobutyl-2)-fluorene	2	Rfl	Ae	0.056	0.084 mol $LiAlH_4$	—	242—243 HCl	73%
9-(1-aminobutyl-2)-thiaxanthene	2	Rfl	Ae	0.1	0.15 mol $LiAlH_4$	—	243—244 HCl	89.0%
11-(1-aminobutyl-2)-6,11-dihydro-dibenzo-[b,e]-oxepine	2	+10	Ae	0.0667	0.1 mol $LiAlH_4$	—	219—220 HCl	87%

The nitriles (II) used as starting materials in which R_1 and R_2 are both hydrogen atoms are obtained in the following way from the nitriles (II) in which R_1 and R_2 together form an additional valency bond.

11-(cyanomethyl)-6,11 - dihydro - dibenzo-[b,e]-oxepine.

A saturated solution of mercuric chloride is prepared in 150 ml. dry ether. After the addition of 12 g. aluminium filings, the solution is left to stand for 3—5 minutes and, after shaking up twice, is decanted. The aluminium amalgamated in this manner is now washed several times with anhydrous ether and finally covered with 300 ml. ether in a stirring apparatus. This is subsequently mixed with 12 g. 11-(cyanomethylene)-6,11-dihydro-dibenzo-[b,e]-oxepine (0.051 mol), prepared as described in C), and 12 ml. water added thereto in the course of 5 hours, while stirring vigorously. The reaction mixture is then left to stand over-night. The inorganic material is filtered off with suction, the filtrate evaporated in a vacuum and 11.5 g. (95.5% of theory) of almost pure product thereby obtained; m.p. 85—86°C. After recrystallising once from a petroleum fraction with a boiling range of 100—140°C., the melting point of the 11-(cyanomethyl)-6,11-dihydro-dibenzo-[b,e]-oxepine obtained increases to 87—89°C. The UV-spectrum shews the absence of the cross-conjugated double bond.

In an analogous manner, there are obtained the following nitriles used as starting materials in which R_1 and R_2 are both hydrogen atoms:

TABLE VII

Compound	m.p. °C.	solvent	yield
9-cyanomethylfluorene	134—135	EA	92%
9-cyanomethylxanthene	140—141	isopr	94.2%
9-cyanomethylthiaxanthene	72—73	PF	91%
5-cyanoethyl-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene	91—92	isopr	88.0%
5-cyanomethyl-5H-dibenzo-[a,d]-cycloheptene	102—103	PF	89.0%
11-cyanomethyl-6,11-dihydro-dibenzo-(b,e)-thiepine	124—126	ethanol	94.5%
9-(1-cyanopropyl-1)-fluorene	81—82	isopr	69.5%
9-(1-cyanopropyl-1)-xanthene	113—114	benzine	72.0%
9-(1-cyanopropyl-1)-thiaxanthene	101—102	isopr	84.5%
9-(1-cyanopropyl-1)-6,11-dihydro-dibenzo-[b,e]-oxepine	b.p. 165—170/0.2	—	81.2%

E) Preparation of compounds (I) in which R_1 and R_2 both represent hydrogen atoms by the subsequent hydrogenation of compounds (I) in which R_1 and R_2 together represent and additional valency bond.

EXAMPLE 49.

5-(2-aminoethyl)-10,11-dihydro-5H - dibenzo-[a,d]-cycloheptene.

23.5 g. 5-(2-aminoethylidine-1)-10,11-dihydro-5H-dibenzo-[a,d] - cycloheptene (0.1 mol), prepared as described in C), are dissolved in 150 ml. alcohol and, after the addition of a small piece of sodium hydroxide, hydrogenated in the presence of 3 g. Raney nickel at a hydrogen pressure of 5 atmospheres. The catalyst is then filtered off, the solvent evaporated and the oily residue distilled in a high vacuum. There are obtained 18.7 g. (79% of theory) 5-(2-aminoethyl)-10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene with a boiling point of 148—149°C. 10.1 mm.Hg. The corresponding hydrochloride melts at 237—238°C.

F) Preparation of compounds (I) in which R_1 and R_2 are both hydrogen atoms by the hydrogenation of compounds (II) in which R_1 and R_2 together represent an additional valency bond.

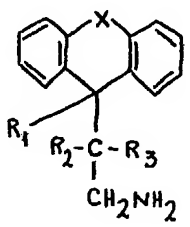
EXAMPLE 50.

9-(2-aminoethyl)-fluorene.

20 g. cyanomethyl-fluorene (0.1 mol), prepared as described in D), are hydrogenated without the use of pressure in alcoholic solution (100 ml.) after the addition of 4 g. Raney nickel, 25 ml. of saturated ammoniacal alcohol and a small piece of sodium hydroxide. The catalyst is thereafter filtered off and the filtrate evaporated to give a dark-coloured, oily residue which dissolves in 1N hydrochloric acid. After extraction with ether, the base is liberated wit 2N sodium hydroxide solution and then distilled in a high vacuum. There are thus obtained 14 g. (67% of theory) 9-(2-aminoethyl)-fluorene which has a boiling point of 131°—135°C./10.2 mm.Hg. The hydrochloride thereof, after recrystallisation from isopropanol, melts at 233—234°C.

WHAT WE CLAIM IS:—

1. Tricyclic ethylamine derivatives of the general formula:—



wherein X is an oxygen or sulphur atom or a saturated or unsaturated, straight or branched chain hydrocarbon radical containing 2 or 3 carbon atoms or an oxaethylene, thiaethylene, thiapropylene or carbonyl group or a valency bond, R_3 is a hydrogen atom or an alkyl radical containing up to 3 carbon atoms, R_1 is a hydrogen atom or a hydroxyl group and R_2 is a hydrogen atom or R_1 and R_2 together represent a further valency bond, with the proviso that when X is an ethylene radical, then R_1 and R_2 are either both hydrogen atoms or together form a further valency bond.

2. 9-Hydroxy-9 - (2 - aminoethyl) - thiaxanthene.

3. 9-Hydroxy-9-(2-aminoethyl)-fluorene.

4. 5-Hydroxy-5 - (2 - aminoethyl) - 5H-dibenzo-[a,d]-cycloheptene.

5. 11-Hydroxy-11-(2-aminoethyl) - 6,11-dihydrodibenzo-[b,e]-oxepine.

6. 11-Hydroxy-11-(2 - aminoethyl) - 6,11-dihydrodibenzo-[b,e]-thiepine.

7. 12 - Hydroxy-12 - (2 - aminoethyl)-5,6,7,12-tetrahydro - dibenzo - [a,d] - cyclooctene.

8. 12-Hydroxy-12-(2 - aminoethyl) - 7,12-dihydro-6H-dibenzo-[b,e]-thiocine.

9. 10 - Hydroxy - 10 - (2 - aminoethyl)-anthrone.

10. 9-Hydroxy-9 - (1 - aminobutyl - 2)-fluorene.

11. 9 - Hydroxy - 9 - (1 - aminobutyl - 2)-xanthene.

12. 9 - Hydroxy - 9 - (1 - aminobutyl - 2)-thiaxanthene.

13. 5 - Hydroxy - 5 - (1 - aminobutyl - 2)-5H-dibenzo-[a,d]-cycloheptene.

14. 11-Hydroxy-11-(1 - aminobutyl - 2)-6,11-dihydrodibenzo-[b,e]-oxepine.

15. 11-Hydroxy-11-(1 - aminobutyl - 2)-6,11-dihydrodibenzo-[b,e]-thiepine.

16. 12-Hydroxy-12-(1 - aminobutyl - 2)-5,6,7,12-tetrahydro-dibenzo - [a,d] - cyclooctene.

17. 11 - (1 - Aminobutylidene-2) - 6,11-dihydro-dibenzo-[b,e]-oxepine.

18. 5-(1 - Aminobutylidene-2) - dibenzo-[a,d]-cycloheptene.

19. 9-(1-Aminoethylidene)-fluorene.

20. 9-(1-Aminoethylidene)-xanthene.

21. 9-(1-Aminoethylidene)-thiaxanthene.

22. 5 - (1 - Aminoethylidene) - 10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

23. 5-(1-Aminoethylidene)-5H - dibenzo-[a,d]-cycloheptene.

24. 11 - (1 - Aminoethylidene) - 6,11-dihydro-dibenzo-[b,e]-oxepine.

25. 11 - (1 - Aminoethylidene) - 6,11-dihydro-dibenzo-[b,e]-thiepine.

26. 12 - (- 1-Aminoethylidene) - 5,6,7,12-tetrahydro-dibenzo-[a,d]-cyclooctene.

27. 9 - (1 - Aminobutylidene - 2)-fluorene.

28. 9 - (1 - Aminobutylidene - 2) - thiaxanthene.

29. 5 - (1 - Aminobutylidene - 2) - 10,11-dihydro-5H-dibenzo-[a,d]-cycloheptene.

30. 11 - (1 - Aminobutylidene - 2) - 6,11-dihydro-dibenzo-[b,e]-ethiepine.

31. 12 - (1 - Aminobutylidene-2)-5,6,7,12-tetrahydrodibenzo-[a,d]-cyclooctene.

32. 9-(1-Aminobutylidene-2)-xanthene.

33. 11-(1-Aminobutyl-2) - 6,11 - dihydro-dibenzo-[b,e]-oxepine.

34. 9-(2-Aminoethyl)-xanthene.

35. 9-(1-Aminobutyl-2)-xanthene.

36. 9-(2-Aminoethyl-1)-fluorene.

37. 9-(2-Aminoethyl)-thiaxanthene.

38. 5-(2-Aminoethyl)-10,11-dihydro - 5H-dibenzo-[a,d]-cycloheptene.

39. 5-(2 - Aminoethyl) - 5H - dibenzo-[a,d]-cycloheptene.

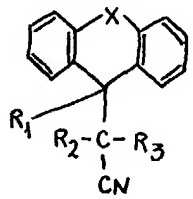
40. 11-(2-Aminoethyl)-6,11-dihydro - 5H-dibenzo-[b,e]-oxepine.

41. 11 - (2 - Aminoethyl) - 6,11 - dihydro-dibenzo-[b,e]-thiepine.

42. 9-(1-Aminobutyl-2)-fluorene.

43. 9-(1-Aminobutyl-2)-thiaxanthene.

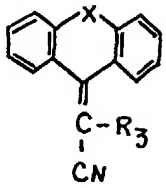
44. Process for the preparation of compounds according to claim 1, wherein a nitrile of the general formula:—



in which R_1, R_2, R_3 and X have the same meanings as in claim 1, is reduced and the compound obtained, in the case in which R_1 is a hydroxyl group, then, if desired, subsequently dehydrated or, in the case in which R_1 and R_2 together represent an additional valency bond, then, if desired, subsequently hydrogenated.

45. Process according to claim 44, wherein the substituents R_1 and R_2 in the starting material have the same significance as desired in the end product.

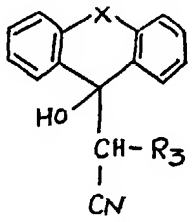
46. Process according to claim 44 or 45 for the preparation of compounds in which R_1 and R_2 together represent an additional valency bond, wherein a nitrile of the general formula:—



in which R_3 and X have the same meanings as in claim 1, is reduced with a complex metal hydride.

47. Process according to claim 44 for the preparation of compounds in which R_1 and R_2 are both hydrogen atoms, wherein a nitrile of the general formula given in claim 46 is reduced catalytically.

48. Process for the preparation of compounds according to claim 1 in which R_1 and R_2 either together represent an additional valency bond or each represent a hydrogen atom, wherein a nitrile of the general formula:—



in which R_3 and X have the same meanings as in claim 1, is reduced and thereafter dehydrated, whereupon, if desired, the compound obtained is hydrogenated.

49. Process for the preparation of compounds according to claim 1, substantially as hereinbefore described and exemplified.

50. Compounds according to claim 1, whenever prepared by the process according to any of claims 44—49.

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